PERSISTENCE OF POLIOVIRUS NEUTRALIZING ANTIBODIES FOUR YEARS AFTER IMMUNIZATION WITH LIVE ATTENUATED VACCINE

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In 1964, this laboratory studied the booster effect of two doses of trivalent oral poliovirus vaccine (OPV) in children previously immunized with formalin-inactivated vaccine (IPV). Five weeks after the second dose of OPV, 99, 100 and 97 per cent of the original 200 children studied had detectable antibodies to poliovirus types 1, 2, and 3, respectively. Four years later as many as possible of the original study population were bled, and poliovirus neutralizing antibody titers were redetermined. A majority of the population was found to have neutralizing antibody titers of 1:16 or greater for poliovirus types 1 and 2, but over half the study group had titers below this level for type 3.

MATERIALS AND METHODS

Study population. The original study population as described by McCollough et al. (1) consisted of 200 children from the first, second, and third grades of three public schools in Columbia, Missouri. In 1968, letters were sent to all of the parents of the original study group requesting permission to rebleed their children and asking for a history of poliovirus immunization since 1964.

Ninety-nine children who had not received any poliovirus vaccine subsequent to the original investigation were included in the study.

SEROLOGY. Serum samples obtained from the 99 children in 1964 (five weeks after the second dose of vaccine) had been stored in screw cap vials at -20 C; they were
thawed and matched with serum samples from 1968. Sera from both years were tested at the same time, and if the original antibody titers as determined in 1964 did not agree with those obtained on retesting of the same sera, the titers of both the 1964 and 1968 sera were retested.

Neutralizing antibody titrations were performed in microtiter plates as previously described (2) except the lowest serum dilution was 1:4 instead of 1:8. The antigens used were the Brunhilde strain of poliovirus type 1, the MEF-1 strain of poliovirus type 2, and the Saukett strain of poliovirus type 3. The challenge dose of live virus in the tests ranged from 63 to 500 TCID₆₀.

RESULTS

The geometric mean antibody titers (GMT) to each of the three poliovirus types were determined from tests performed in 1968. On sera drawn in 1964, five weeks after the second dose of OPV, the GMT's were 113, 356, and 61 for poliovirus types 1, 2, and 3, respectively. On sera drawn in 1968, four years after the second dose of OPV, the GMT's were 30, 54, and 12 for the three types, respectively. It is apparent that the mean titer for poliovirus type 2 was higher both at five weeks and at four years after immunization than the GMT for the other two poliovirus types. At both periods of time the GMT for poliovirus type 3 was the lowest.

Five weeks after the second dose of OPV, neutralizing antibodies (≥1:4) were found in 97 per cent of the children for type 1 and in 98 per cent for type 3. All children had antibodies to type 2. Four years after immunization, detectable neutralizing antibodies (≥1:4) were present in 97 per cent of the children for type 1 and in 87.9 per cent for type 3. Again, all children had antibodies for type 2.

Five weeks after the second dose of OPV, antibody titers of 1:16 or greater were found in 93.9 per cent of the population for type 1, in 100 per cent for type 2, and in 90.9 per cent for type 3. Four years later, 77.8 per cent, 97 per cent, and 45.5 per cent of the population had neutralizing antibody titers of 1:16 or greater for types 1, 2, and 3, respectively.

Comparing neutralizing antibody titers in the 1964 sera (as determined in 1968) with titers in the 1968 sera, a fall of two or more dilutions could be demonstrated for type 1 antibodies in 60.6 per cent of the sera. A similar fall was found for type 2 antibodies in 76.8 per cent of the sera, and for type 3 antibodies in 71.7 per cent of the sera. These data are summarized in table 1.

As a means of indicating the rate of decline of neutralizing antibody titers, coefficients of regression were calculated. The coefficient for type 1 was .570, for type 2 was .452, and for type 3 was .341. To quantitate the relationship between antibody titers five weeks postimmunization and those four years later, linear coefficients of regression were calculated as

<table>
<thead>
<tr>
<th>Category</th>
<th>Poliovirus type</th>
</tr>
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<tbody>
<tr>
<td>Percentage of population with detectable titers 5 weeks after immunization</td>
<td>1</td>
</tr>
<tr>
<td>97.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage of population with detectable titers 4 years after immunization</td>
<td>97.0</td>
</tr>
<tr>
<td>Percentage of population with titers of 1:16 or greater 5 weeks after immunization</td>
<td>93.9</td>
</tr>
<tr>
<td>Percentage of population with titers of 1:16 or greater 4 years after immunization</td>
<td>77.8</td>
</tr>
<tr>
<td>Percentage of population with significant falls in titer between 5 weeks and 4 years postimmunization</td>
<td>60.6</td>
</tr>
</tbody>
</table>

Table 1
Persistence of neutralizing antibodies to poliovirus types 1, 2, and 3 following immunization with trivalent oral poliovirus vaccine
shown in figure 1. Regression analysis showed that variation due to regression was significant (alpha <= .01) for all three types of poliovirus. It should be noted that subjects with lower titers in 1964 had a relatively slight drop in antibody level over the four years, while those with high titers in 1964 had proportionately greater drops.

Comparison of the neutralizing antibody titers in the same sera before and after four years of storage showed a fall in titer of two or more dilutions in 5 per cent of the sera for type 1, 16.2 per cent for type 2, and 12.1 per cent for type 3. On the other hand, there was a rise in titer of two or more dilutions with storage in 6 per cent of the sera for type 1, 6 per cent for type 2, and 2 per cent for type 3.

During the period of the study one child developed neutralizing antibodies to type 1 and another to type 3; a third child had an increase in titer to poliovirus type 3 from 1:32 to 1:128. No cases of poliomyelitis were reported from this area during the time of the investigation.

DISCUSSION

It appears from our results that neutralizing antibody titers four years after immunization with trivalent oral poliovaccine are adequate in children previously immunized with IPV. However, serum antibody is only one phase of host resistance and does not necessarily reflect the state of all the protective mechanisms.

Four years after oral immunization, 77.8 per cent of the population had neutralizing antibody titers of at least 1:16 for type 1, 97 per cent for type 2, and 45.5 per cent
for type 3; and only 3 per cent, 0 per cent, and 12 per cent had no detectable neutralizing antibodies for types 1, 2, and 3, respectively. The GMT for all three polioviruses dropped rather markedly in the four years following immunization; therefore, it would seem prudent to recommend a booster dose of OPV to previously immunized individuals who are traveling to areas where poliovirus is prevalent or when there is an epidemic of poliomyelitis in the community.

The need for future investigations of long term immunity following immunization with OPV is emphasized by the high percentage of the children with low levels of antibody to type 3 poliovirus four years after immunization. Type 3 antibody titers were lower five weeks after immunization than titers to either poliovirus type 1 or poliovirus type 2 (GMT for type 1 was 113, for type 2 was 356, and for type 3 was 61). Because of this fact and because of the 12 per cent of the population without detectable neutralizing antibody titers for poliovirus type 3, four years after the last OPV was given, it would seem that protection against type 3 poliovirus could be less durable following immunization than that for the other two types.

Of interest is the fact that in the years 1964 through 1967, 20 cases of paralytic poliomyelitis have been reported (3, 4) in the United States after adequate IPV vaccination had been received. In 12 of these the causative poliovirus was identified. Six cases were associated with poliovirus type 3, five with type 1, and one with type 2. In this same time interval, 17 cases of paralytic polio occurred following adequate immunization with monovalent OPV (3, 4). Information is available concerning the causative poliovirus for only two of these cases. One was attributed to type 3 and one to type 2. Only one case of paralytic disease has been reported following adequate immunization with trivalent OPV and type 1 was found to be the cause (4). The occurrence of these cases provides evidence that paralytic disease can follow supposedly adequate vaccination.

Other investigators have examined antibody titers at long intervals following immunization. Lepow and co-workers (5) found that 96 per cent of their study group, two years after immunization had titers of at least 1:8 to all three poliovirus types. Cabasso and co-workers (6) determined that 81.3 per cent, 100 per cent, and 94.6 per cent of originally seronegative children had retained titers of 1:16 or greater to types 1, 2, and 3, respectively, three years after immunization.

Unfortunately, our data do not bear on the disputed question as to whether the persistence of antibodies after OPV is any different from the persistence of antibodies following IPV. Furthermore, we do not know of any study which has directly attacked this question.

Upon comparing neutralizing antibody titers before and after four years of storage at —20 C, we concluded that such antibodies were relatively stable under these conditions. Only 5.1 per cent, 16.1 per cent, and 10.1 per cent of the titers to poliovirus types 1, 2, and 3, respectively, declined by two or more dilutions during this interval, but there was a rise in titer of two or more dilutions in 6 per cent of the sera for type 1, 6 per cent for type 2, and 2 per cent for type 3. Variability inherent in the microtiter method makes it difficult to compare antibody titers determined at different times. The fact that a number of sera had rises in titer indicated this variability was probably responsible for some of the apparent falls in antibody level. Extrapolating from this, the neutralizing antibodies were most likely more stable than our data indicate.

References


